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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,729	03/15/2004	Peter N. Kao	STAN-352	1829

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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	**PAPER NUMBER**
1614	

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05/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/801,729	KAO ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,10-24,30,32,33 and 36-39* is/are pending in the application.

4a) Of the above claim(s) *11 and 14-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,10,12,13,19-24,30,32,33 and 36-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Acknowledgement is made of applicant's filing of an amendment/remarks and Declaration under 37. CFR 1.132 on 02/20/2007. By the amendment, claims 2, 9, 25-29 and 34-35 have been cancelled and claims 1, 3, 8, 10, 19, 20, 22, 23-24, 30, 32, 33 and 36-39 have been amended. Claims 1, 3-8, 10, 12-13, 19-24, 30, 32-33 and 36-39 are currently pending for prosecution on the merits of the case.

2. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1, 3-8, 10, 12-13 and 19-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites that the HMG-CoA reductase inhibitor is present in amounts "which does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient". The specification does not provide a standard for ascertaining the requisite degree of "does not substantially increase...", and one of ordinary skill

in the art would not be reasonably apprised of the scope of the invention. Applicant is requested to clarify.

The applicant could overcome this rejection by canceling "substantially" in claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 3-8, 10, 12, 19-22, 30, 32-33 and 38-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Liao et al. (WO 00/56403).

Liao teaches the use of HMG-CoA reductase inhibitor such as simvastatin in treating pulmonary arterial hypertension or thromboembolism or increasing blood flow in tissue of a subject alone (page 13, line 19 thru page 14, line 1; page 16, line 2 thru page 17, line 7) or in combination with other active agent such as prostaglandin (page 24, line 16), wherein the simvastatin is administered in 0.01 mg/kg per day to 1000 mg/kg per day (page 10, lines 5-8), in various dosage forms including oral, rectal, topical, nasal, interdermal or patenteral (page 21, lines 3-11.

With respect to the activity of simvastatin in "in an amount effective to reduce vascular occlusion in the pulmonary arteries of the patient, and which does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient" (claim 1), "neointimal smooth muscle cell hyperplasia is decreased" (claim 19), "the

blood flow is increased by from about 5% to at least aboue 300%" (claim 21) or "reversing right ventricular hypertrophy" (claim 30), such properties or characteristics deems to be inherent to the referenced method since the administration of same compound (i.e., simvastatin) in overlapping dosage amount inherently possessing therapeutic effect for the same ultimate use as disclosed by the applicant anticipates the claimed invention even absent explicit recitation of underlying mechanism.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 13, 23-24 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liao et al. (WO 00/56403).

With respect to claims 23-24 and 36-37,

The teaching of Liao has been discussed in above 35 USC 102 (b) rejection.

Liao differs from the claimed invention in various dosage delivery forms including pulmonary, oral, transmucosal, transdermal and parenteral administration, particularly via inhalation administration (e.g., powder inhaler, metered dose inhaler and nebulizer).

However, those of ordinary skill in the art would have been readily optimized effective delivery forms as determined by good medical practice and the clinical condition of the individual patient. Determination of the appropriate delivery dosage forms for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the conventional drug delivery forms known in pulmonary hypertension treatment of art.

With respect to claim 13,

The teaching of Liao has been discussed in above 35 USC 102(b) rejection.

The teaching of Liao differs from the claimed invention in the selection of prostacyclin. However, one having ordinary skill in the art would have been motivated to select the claimed

compound with the expectation that prostacyclin would not significantly alter the analogous properties of the compound of the reference due to close similarity of the compounds.

Response to Arguments

6. Applicant's arguments filed 02/20/07 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position that the term "which does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patients" refers to an increases of NOS expression or activity to levels which would exist in normal healthy endothelial tissue, but not to any enahancement of NOS expression or activity above levels that would exist in normal healthy endothelial tissue. Applicant alleges that it is well within the skill set of an ordinary practitioner to determine the NOS expression levels that are exhibited by normal healthy endothelial tissues, especially in light of Example 5.

This argument is not found persuasive. Although the specification discloses assay method (e.g., Western immunblotting technique or RT-PCR) in measuring endothelial cell nitric oxidase synthase levels, the specification does not clearly provide a standard for ascertaining the requisite degree of "does not substantially increase", and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is considered that the meaning of the claims should be clear from the wording of the claim alone.

Applicant's argument in the response takes the position that Liao does not teach the step of administering an amount of a HMG-CoA reductase inhibitor that is effective to reduce

vascular occlusion in the pulmonary arteries but does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries. Applicant alleges that the Liao's teaching in increasing endothelial nitric oxide synthase activity is in fact the contrary to the instant invention.

This argument is not found persuasive. Anticipation under 35 USC 102 is an essentially irrebuttable question of fact, wherein the court stated that anticipation "cannot be overcome by evidence of unexpected results or teachings away in the art". *In re Malagari, 499 F.2d 1289, 182 USPQ; In re Spada, 911 F.2d 705, 15 USPQ2d 1655 (Fed. Cir. 1990); In re Fracalossi, 681 F.2d 792, 215 USPQ 569 (CCPA 1982); In re Alternpohl, 500 F.2d 1151, 183 USPQ 38 (CCPA 1974); In re Wiggins, 488 F.2d 538, 179 USPQ 421 (CCPA 1973); In re Wilder, 429 F.2d 447, 166 USPQ 545 (CCPA 1970).* Indeed, a reference might reside in a nonanalogous art and yet constitute an anticipation of a claimed invention under 35 USC 102. *In re Self, 571 F.2d 134, 213 USPQ 1 (CCPA 1982).* Thus, as discussed above, the administration of same compound (i.e., simvastatin) in overlapping dosage amount inherently possessing therapeutic effect for the same ultimate use as disclosed by the applicant anticipates the claimed invention even absent explicit recitation of underlying mechanism.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. No Claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system,

see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Brian Kwon
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